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D E C I S I O N
of 28 August 2003

Case Number: T 0286/01 - 3.3.4

Application Number: 91901433.2

Publication Number: 0460167

IPC: C12P 21/08

Language of the proceedings: EN

Title of invention:
Humanised Antibodies

Patentee:
CELLTECH THERAPEUTICS LIMITED

Opponent:
Protein Design Labs, Inc.

Headword:
Humanised antibodies/CELLTECH THERAPEUTICS LTD.

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
"Allowability of amendments (no)"

Decisions cited:
T 0823/96

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0286/01 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 28 August 2003

Appellant: (Proprietor of the patent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 1 March 2001 revoking European patent No. 0460167 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairman: U. Kinkeldey
Members: M. Wieser
S. Hoffmann

Summary of Facts and Submissions

I. The appeal was lodged by the patent proprietors (appellants) against the decision of the opposition division, whereby the European Patent No. 0 460 167 was revoked pursuant to Article 102(1) EPC. The patent had been opposed by one party under Articles 100(a), (b) and (c) EPC. The opposition division found that claim 1 of a main request and of an auxiliary request before them contained subject-matter which extended beyond the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

II. The appellants requested that the decision under appeal be set aside and the patent be maintained on the basis of the main or auxiliary request both filed on 3 July 2001. Once a set of claims meeting the requirements of Article 123 EPC was allowed, the case should be remitted to the first instance for further prosecution.

The opponents (respondents) requested that the appeal be dismissed.

III. Claim 1 of the main request, which is identical to claim 1 of the auxiliary request before the opposition division, reads:

"An antibody molecule having affinity for a predetermined antigen and comprising a composite heavy chain and a complementary light chain, said composite heavy chain having a variable domain comprising acceptor antibody heavy chain framework residues and donor antibody heavy chain antigen-binding residues, said donor antibody having affinity for said

predetermined antigen, wherein, according to the Kabat numbering system, in said composite heavy chain, amino acid residues 5, 8, 10, 12 to 17, 19, 21, 22, 40, 42 to 44, 66, 68, 70, 74, 77, 79, 81, 83 to 85, 90, 92, 105, 109, 111 and 113 at least are acceptor residues and amino acid residues 23, 24, 31 to 35, 49 to 65, 71, 73, 78 and 95 to 102 at least are donor residues."

Claim 1 of the auxiliary request differs therefrom only in so far as the donor residues are defined as: ".. amino acid residues 23, 24, 26 to 35, 49 to 65, 71, 73, 78 and 95 to 102 at least are donor residues".

IV. The arguments of the appellants may be summarised as follows:

The patent disclosed humanised antibodies which overcame the disadvantages of antibodies of rodent origin (HAMA response) and of CDR-grafted antibodies (low binding affinity). For reaching this target, the skilled person gets the genuine teaching to start with an acceptor (human) antibody (pages 16 and 19), to replace the acceptor CDRs by donor CDRs and to choose from the list of all possible residues mentioned on pages 6 to 23 of the application as originally filed additional amino acid residues of the acceptor antibody and replace them by the respective donor residues.

The selection of obligatory donor residues according to claim 1 was disclosed on page 7, lines 1 to 3 of the original application.

Although the application did not explicitly refer to amino acid residues that obligatorily remained acceptor residues, this feature of claim 1 had implicit support in the application as originally filed. Since the starting point for the production of the claimed antibodies was an acceptor molecule, by definition all amino acid residues not mentioned in pages 6 to 23 as being donor residues, had to be acceptor residues. The 32 amino residues designated in claim 1 as being acceptor residues, corresponded exactly to those of the 113 amino acids of the variable domain of the heavy chain which were not mentioned as possible donor residues on pages 6 to 23 of the application as originally filed.

V. The arguments of the respondents may be summarised as follows:

Chronic inconsistency between different parts of the patent specification (description, claims, and examples) made it impossible to find a basis for any of the features contained in claim 1 of both requests. Considering that the open-ended formulation of the claim indicated a minimum number of obligatory donor and acceptor claims only, that the originally filed application missed any reference to a residue being obligatorily acceptor and that the antibodies disclosed in the examples lied outside the scope of the claim, the patent specification did not contain a statement that allowed to write a claim like present claim 1 under the requirements of Article 123(2) EPC.

Reasons for the Decision

Main request
Article 123(2) EPC

1. Claim 1 refers to an antibody molecule characterised by a specific heavy chain variable domain. It is generally known and not disputed between the parties that this domain consists of 113 amino acid residues and contains three complementarity determining regions (CDRs). Amino acids lying outside the CDRs form the so-called framework region.

The heavy chain variable domain according to claim 1 is characterised by comprising antibody framework residues from an acceptor and antibody antigen-binding residues from a donor, wherein **at least** 32 precisely defined framework amino acids are acceptor residues and **at least** the three CDRs plus 6 precisely defined framework amino acids are donor residues.

2. The patent in suit refers to "CDR-grafted antibodies" (see for instance page 6, second and third paragraph of the application as originally filed), defining antibodies wherein the original acceptor CDR's have been replaced by CDR's derived from a donor antibody.

According to page 6, lines 14 to 21 of the original application, the present inventors "... have further investigated the preparation of CDR-grafted humanised antibody molecules and have identified a hierarchy of positions within the framework region of the variable regions ... at which the amino acid identities of the

residues are important for obtaining CDR-grafted products with satisfactory binding affinity."

3. From page 6 to page 23 of the application as originally filed, 81 amino acid residues, comprising the three CDR's (amino acids 31 to 35, 50 to 65 and 95 to 102) of the heavy chain variable domain are indicated as possible members of the "hierarchy of positions" mentioned above.

According to claim 1 the three CDR's plus amino acids 23, 24, 49, 71, 73 and 78 are derived from the donor antibody. This corresponds to what is described on page 7, lines 1 to 3 of the originally filed application as being a preferred embodiment of the invention.

4. It is submitted by the appellants that there is no explicit basis for the recitation of the acceptor residues of claim 1 in the application as originally filed. However, the appellants take the view, that a skilled person having followed pages 6 to 23 of the description, and having changed all acceptor residues to donor residues at all the places mentioned, would automatically consider a list of exactly the 32 amino acid residues listed in claim 1 as being acceptor residues. Thus, in the appellants view, the group of acceptor residues recited in claim 1 is implicitly disclosed in the application as originally filed.

5. The board does not agree. Appellant's line of argumentation is contradictory to the case law of the Boards of Appeal.

In the decision T 823/96 (28 January 1997) the criteria for implicit disclosure were developed as follows (point 4.5 of the reasons for the decision):

*".. the term "implicit disclosure" should **not** be construed to mean matter that does not belong to the **content** of the technical information provided by a document but may be rendered **obvious** on the basis of that content. In the Board's judgement, the term "implicit disclosure" relates solely to matter which is not explicitly mentioned, but is a clear and unambiguous consequence of what is explicitly mentioned. Therefore, whilst common general knowledge must be taken into account in deciding what is clearly and unambiguously implied by the explicit disclosure of a document, the question of what may be rendered obvious by that disclosure in the light of common general knowledge is not relevant to the assessment of what is implied by the disclosure of that document. On the contrary these two questions must be strictly separated."*

6. In the present case 32 of the 113 amino acid residues of an antibody heavy chain variable domain **are not explicitly mentioned** in "a hierarchy of positions within the framework of the variable regions ... at which the amino acid identities of the residues are important for obtaining CDR-grafted products with satisfactory binding affinity" (page 6, lines 15 to 21 of the application as originally filed). There is no disclosure that a specific amino acid residue **must not** be included into said hierarchy. Therefore it is not the clear and unambiguous consequence of what is explicitly disclosed in the application as originally

filed that these 32 residues have to be acceptor residues as required by claim 1. Rather, the conclusion a skilled reader can draw from the fact that specific amino acid residues are not explicitly mentioned in the "hierarchy of positions" as originally filed is that these residues can be both, either acceptor or donor.

7. Accordingly, the Board does not see a basis in the application as originally filed for claim 1 referring to a humanised antibody comprising a heavy chain variable domain wherein specific amino acid residues are acceptor residues. The claim under consideration thus, does not meet the requirements of Article 123(2) EPC with the consequence that the main request is not allowable.

Auxiliary request
Article 123(2) EPC

8. Claim 1 of the auxiliary request differs from that of the main request in so far as other donor residue positions are defined. With regard to the acceptor residue positions the claim is identical to claim 1 of the main request (see section III supra). The reasons given above for claim 1 of the main request equally apply for claim 1 of this request which, thus, also contravenes the requirements of Article 123(2) EPC . Accordingly the auxiliary request is not allowable either.

Order

For these reasons it is decided:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey